REMARKS

Claims 1, 3-7 and 12-23 are pending and under examination. Applicants note the Examiner' acknowledgement of the claim to foreign priority in this application.

Rejections under 35 USC § 103(a)

Claims 1, 3-7, 12, 14, and 22 are rejected as unpatentable over WO 01/078693 ("Staniforth") in view of U.S. 6,521,260 ("Vectura"). The rejection is traversed

Claim 1, the sole independent claim, is directed to a dry powder formulation for inhalation. The amended claim specifies that the dry powder formulation comprises active particles, carrier particles, and magnesium stearate in an amount of at least 0.5% by weight of the formulation, wherein the particles of magnesium stearate are disposed on the surface of the carrier particles, and wherein the coverage of the magnesium stearate on the surface of the carrier particles is less than 5%.

Staniforth is relied upon for its description of a powder formulation for use in a multidose dry powder inhaler, the formulation comprising an active agent, carrier particles, and magnesium stearate in an amount from 0.02% to 1.5% by weight of the formulation. Office action at p. 3, para. 2 (citing to Staniforth at p. 14, lines 12-17). While the claimed range falls within this broad range recited by Staniforth, the skilled person would have lacked a reasonable expectation of success in making a dry powder formulation comprising at least 0.5% by weight of magnesium stearate based on Staniforth. This is because, at the time of the invention, it was also commonly understood that only small amounts of additive and "particularly small amounts" of magnesium stearate as additive should be used to coat carrier particles for DPI powders. Vectura at col. 3, lines 56-60. Vectura expressly teaches away from using magnesium stearate as an additive in an amount of 1.5% by weight (based upon the weight of the formulation), stating that this amount causes premature segregation of active particles from the carrier particles. Vectura col. 2 line 61 to col. 3 line 1. Vectura does not specify the amount of magnesium stearate that can be used, nor does Vectura exemplify a dry powder formulation containing magnesium stearate. However, WO 2000/53157 ("Chiesi") specifies that the amount of magnesium stearate is less than 0.5%. Staniforth is consistent with Vectura and Chiesi in describing the amount of magnesium stearate

as not more than 1.5% and most preferably between 0.2 and 0.4%. Indeed, as noted in Applicants' specification, an article published by Staniforth in 1982 indicates that the use of magnesium stearate in amounts of 0.5% to 4% de-stabilizes the powder formulation causing significant segregation of active particles from carrier particles. *See* specification at p. 3, lines 1-4, citing Staniforth et al., *J. Pharm. Pharmacol.* 1982 34:141-145 (C5 of IDS filed 9/29/10). The Examples of Staniforth itself discourage the skilled person from using magnesium stearate in amounts of more than 0.5% since higher amounts reduce the fine particle fraction (FPF) of the powder (see Table 6 at p. 23 of Staniforth). The skilled person reading Staniforth would observe that all subsequent examples utilize magnesium stearate in amounts less than 0.5% by weight of the formulation (see e.g., Examples 7-12 of Staniforth). Thus, the skilled person would have lacked a reasonable expectation of success in using magnesium stearate in amounts of more than 0.5% as an additive to the coat carrier particles of a DPI formulation based upon Staniforth.

Staniforth is further relied upon for describing a surface coverage of the carrier particles that is "at least 5%". Office action at p. 3. Staniforth does not describe or suggest a formulation comprising carrier particles wherein the coverage of the magnesium stearate on the surface of the carrier particles *is less than 5%*, as required by claim 1. Moreover, Staniforth explicitly states that the carrier particles of the formulation should have a coverage of *at least 5% and preferably 15%*. Staniforth at p. 11, lines 3-8.

Vectura is relied upon for overcoming the deficiencies of Staniforth regarding a carrier particle coverage of less than 5% by magnesium stearate. The Examiner notes that Vectura describes "a discontinuous coating of the additive [where] the additive material and the carrier particles are mixed for between 0.1 and 0.5 hours." Office action at p. 4, para. 3. The Examiner contends that Vectura teaches that "less coverage of lactose is sufficient to increase the respirable fraction of the active material" and that this would provide the motivation to "try using less than 5% surface coverage with an expectation of the same results as that of Staniforth.

The Examiner's reliance on Vectura for providing the skilled person with the motivation to reduce additive coverage of the carrier particles is misplaced. Contrary to the Examiner's interpretation, Vectura unambiguously directs the skilled person to obtain the highest possible coverage of carrier particles with additive, notwithstanding that this coverage may be discontinuous. Thus, Vectura states that it is preferable for additive to "saturate" the surface of

the carrier particles, meaning that "even if more additive material were provided substantially the same covering would be achieved." Vectura at col. 7, lines 20-24. This is consistent with the understanding in the art at the time of the invention, that higher coverage with less calcium stearate was optimal, as evidenced by WO 2000/53157 ("Chiesi"). Chiesi is also referred to by Staniforth for its description of magnesium stearate particles partially coating the surface of carrier particles. *See* Staniforth at p. 6, lines 19-23. Chiesi teaches that it is desirable to coat as much of the surface of the carrier particles as possible using a small amount of a "lubricant", which is preferably calcium stearate. Chiesi at p. 5 lines 6-9 and p. 6 lines 20-22. Specifically, Chiesi teaches that the coating should be *more than 10%* and preferably *more than 35%*. Chiesi at p. 6, lines 5-12.

In contrast to these descriptions in the prior art indicating that *higher* coverage of the carrier particles with calcium stearate was desirable, Applicant's specification teaches that "[t]he formulations of the present invention are prepared in a manner *to ensure the lowest possible coverage* of magnesium stearate on the carrier particles." Specification at p. 7, lines 25-26. This is based upon Applicants' surprising discovery that the effect of surface coverage on the performance of the dry powders is minor compared to the moisture protection and lubricating properties of the magnesium stearate. Specification at p. 5, lines 4-8. Accordingly, if the surface coverage of the carrier particles by magnesium stearate is kept low, it is possible to employ relatively large amounts of magnesium stearate and still obtain a reproducibly high fine particle fraction. Specification at p. 5, lines 8-12. Thus, absent the teachings of Applicants' specification, the skilled person would have sought to *increase* the coverage of magnesium stearate on the carrier particles and would have had no reason to produce a dry powder formulation wherein the coverage of the magnesium stearate on the surface of the carrier particles *is less than 5%*, as required by amended claim 10.

Response to Examiner

The Examiner stated that Staniforth does not follow Chiesi because Staniforth has "expanded upon the ranges taught by Chiesi." Office action at p. 6. Therefore, in the Examiner's opinion, Chiesi (filed 3/5/99) does not reflect the understanding of the skilled person at the time of Staniforth (filed 4/17/01 priority to 4/17/00). Applicants disagree with the

Examiner's characterization of Staniforth as not following the teachings of Chiesi. Although Staniforth describes ranges slightly outside of Chiesi, the preferred embodiments of Staniforth are within the ranges specified by Chiesi, as discussed above. Thus, Staniforth supports Applicants' position that at the time of the invention, it was commonly understood that higher coverage of the carrier particles with less magnesium stearate was optimal, as described by Chiesi. This is further evidenced by Vectura, as discussed above.

The Examiner further stated that Vectura, published after Staniforth, reflects the "changed knowledge in the art that less coverage of the carrier by an additive such as magnesium stearate still results in an increased respirable fraction of the active material." Office action at p. 7. The Examiner mischaracterizes Vectura. Instead, as discussed above, Vectura is consistent with Chiesi and Staniforth in its teaching that higher coverage with less additive is optimal.

The Examiner further states that Vectura, which generically describes a mixing time of from 0.1 to 0.5 hours "presumably describes a decreased degree of coating" (of the additive on the carrier particles). Office action at p. 7. However, this is contrary to the explicit statements in Vectura that it is desirable to saturate the surface of the carrier particles with additive "in the sense that even if more additive material were provided substantially the same covering would be achieved." Vectura at col. 7, lines 20-24 (emphasis added). Thus, the Examiner's presumption that Vectura describes "a decreased degree of coating" is directly contradictory to the stated purpose of the methods described by Ventura. To the extent that the Examiner's rejection is based upon this presumption, it is without merit.

The Examiner also stated that Applicants have not provided any data to document their unexpected results. However, the data shown in Examples 1-5 of Applicants' specification shows that powder formulations having relatively high amounts of magnesium stearate (1%, 2%) can be made according to the invention that have a reproducibly high fine particle fraction which is also stabilized against moisture. See the specification at pp. 21-24.

In summary, a dry powder formulation wherein the coverage of the magnesium stearate on the surface of the carrier particles *is less than 5%* is neither disclosed nor suggested by the combination of Staniforth and Vectura. Accordingly, a *prima facie* case of obviousness has not

been established with respect to claim 1, or its dependent claims. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 103 is requested.

Claims 13, 15-21, and 23 are rejected over Staniforth and Vectura in combination with WO 00/28979 ("Keller"). Applicants traverse. Claims 13, 15-21, and 23 each depend from claim 1. Keller is relied upon for its description of the specific active ingredients rectied in the dependent claims. But this description in Keller does not overcome the deficiencies of Staniforth and Vectura discussed above. Accordingly, a *prima facie* case has not been established with respect to these claims, which contain all of the limitations of claim 1. Reconsideration and withdrawal of the rejection is requested.

Double Patenting Rejection

Claims 1, 3-7 and 12-23 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 10 and 24-42 of copending application U.S. Serial No. 12/536,980 in view of Staniforth (WO 01/78693).

Applicants defer addressing the rejection until such time as one or more of the conflicting claims is deemed allowable.

Applicants submit that the application is in condition for allowance and request an action for same. The Commissioner is hereby authorized to charge any additional fees that may be due, or credit any overpayment, to Deposit Account No. 50-0311, Reference No. **28069-625N01US**.

Respectfully submitted,

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